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LS-12-IN-3538 PNCs associate with structure and function of the nucleolus

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The perinucleolar structure is a nuclear body forming in highly malignant cancer cells. To address its structure and function, we employed chemical-biology approaches, in which small molecules that significantly reduce PNC prevalence were identified and used as chemical probes. Compound ML246 disassembles PNCs effectively in the nM range, and inhibits soft agar growth and invasion capability of cancer cells in vitro. In a PC3M human metastatic prostate cancer mouse model, ML246 significantly inhibits the growth of the tumors and blocks the metastasis of PC3M cancer cells into lungs. In a pancreatic cancer model, ML246 blocks metastasis to lung and liver. Thus, PNC disassembly corresponds well with inhibition of malignant behavior of cancer cells both in vitro and in vivo. Cellular and molecular analyses of the mechanism of action show that ML246 induces significant and reversible changes in the nucleolar structure as evaluated both by light and electron microscopy. Correspondingly, ML246 treatment induces reduction of pol I and pol III transcription. However, there is little change in pol II transcription. Gene array analyses show biased impact on gene expression upon treatment. These studies suggest that PNC function directly associates with nucleolar and pol III activities. Experiments are currently underway to identify the cellular pathways by which ML246 reduces PNC, disrupts nucleolar structure, regulates transcriptions, and blocks malignant behavior, so as to tease out the functional relation among all of them.

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